# Epitomes

## Important Advances in Clinical Medicine

# Pediatrics

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*The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.*

*The epitomes included here were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association, and the summaries were prepared under the direction of Susan B. Conley, MD, and the panel.*

## New Antiepileptic Drugs for the Treatment of Childhood Epilepsies

THE GOAL OF THE pharmacologic treatment of childhood epilepsy is to reduce seizure activity and avoid drug toxicity. Meeting this goal has been a challenge because many of the current drugs have potentially serious adverse effects associated with their use, such as bone marrow suppression, liver toxicity, and decline in cognitive function. Therefore, there is a pressing need for new drugs that are effective and safe for use in children.

For the first time since 1978, new antiepileptic drugs have been approved by the US Food and Drug Administration for the treatment of seizures. Although there are several established drugs for treating epilepsies, about 25% of all patients are refractory to medical treatment. New medications are therefore needed for these patients.

Felbamate, introduced in 1993, is the first of the new generation of antiepilepsy drugs to be used in the treatment of childhood epilepsies. It is mainly effective in patients with partial seizures. It is also used to reduce seizure activity in children with the Lennox-Gastaut syndrome—a severe childhood encephalopathy associated with intractable seizures of several types. During experimental trials, this drug was found to be well-tolerated and safe. Common side effects include loss of appetite, weight loss, and insomnia. During the first year of use after its introduction, however, several cases of aplastic anemia and acute hepatic failure have emerged. Because of these serious problems, the use of felbamate is limited to children with severe seizures in whom alternative medications are not effective.

Gabapentin has also been approved for use in the United States in the past two years. It was designed as an analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), but the drug has no effect on the brain GABA system, and the mechanism of its action is unknown. The medication is to be used as an add-on agent in the treatment of refractory partial-onset seizures. Interestingly, this drug is not protein-bound, does not interact with other drugs, and is excreted entirely by the kidneys without undergoing metabolism. It has been approved for use in children older than 12 years. The experience with younger children is limited.

Lamotrigine is a novel drug that appears to be effective for a wide range of seizure types. Its mechanism of action may be related to blocking of the sodium channel and inhibiting the release of the excitatory amino acid glutamate. In children, it appears to be particularly effective for partial seizures, generalized tonic-clonic seizures, absence seizures, and atonic seizures seen in patients with the Lennox-Gastaut syndrome. It has been used by about 80,000 patients in Europe and other countries, and its use is well tolerated by children. Lamotrigine has recently been approved in the United States for use in adults with epilepsy. Dizziness, blurred vision, and ataxia are the most frequent side effects. Rash is the most common side effect leading to discontinuation and occurs particularly frequently when the drug is given with valproic acid. Lamotrigine interacts substantially but predictably with other drugs.

Vigabatrin is another novel agent that appears promising as therapy for children with a wide range of seizure types. Vigabatrin increases brain GABA levels by irreversibly inactivating GABA aminotransferase, an enzyme that breaks down GABA. The drug has been used extensively in Europe and Canada for its apparent effectiveness against infantile spasms, the Lennox-Gastaut syndrome, and partial seizures. In 1983 US clinical trials came to an abrupt halt because this medication caused microvacuolization of the white matter in animals. This has not occurred in humans with exposure to the drug, however, and studies have resumed. Somnolence is the most frequent side effect. Overall, its use is well tolerated, although psychotic symptoms can occur rarely in adults.

Recent advances in antiepileptic drug development hold the promise of substantial improvement in the treat-

ment of childhood epilepsies. Of all the new drugs, lamotrigine and vigabatrin hold the most promise. They have a broad spectrum of efficacy, and their use is well tolerated. They appear to be particularly useful in severe childhood epileptic syndromes. These two drugs should be available soon in the United States for use in children. Considering our inexperience with and possible toxicity of these agents, neurologic consultation is suggested.

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## New Drugs for Cystic Fibrosis Lung Disease

SINCE THE DISCOVERY of the molecular basis for cystic fibrosis with the cloning of the gene in 1989, there has been an explosion of new information on the pathogenesis of the disease. Concomitantly, the development of new therapies based on a better understanding of the pathophysiology of the progressive obstructive airways disease that characterizes the pulmonary component has resulted in rapid, revolutionary changes in management that presage the transformation of this lethal disease into a manageable chronic illness.

The approximate cause of the progressive loss of lung function and, ultimately, the respiratory failure that causes death in more than 95% of patients is a relentless, chronic neutrophilic endobronchitis, usually accompanied by chronic infection with mucoid forms of *Pseudomonas aeruginosa*. Recent studies using bronchoalveolar lavage and analysis of molecules and cells involved in this process have shown the overwhelming importance of a dysregulated acute inflammatory response that causes enormous collateral damage from neutrophil products designed for the intracellular digestion of foreign pathogens. An understanding of the central importance of the frustrated host inflammatory response in causing structural and functional lung damage has led to the hypothesis that the direct suppression of inflammation can, independent of antimicrobial chemotherapy, ameliorate cystic fibrosis lung disease. The Cystic Fibrosis Foundation sponsored a four-year, multicenter, double-blind, placebo-controlled study of the use of alternate-day prednisone in patients with mild lung disease. Although the high-dose arm of 2 mg per kg produced unacceptable side effects, administering the lower-dose arm of 1 mg per kg resulted in sustained improvement in pulmonary function over the entire four-year period in patients colonized with *P aeruginosa*. Growth suppression after two years was the only major toxic effect. Thus, the treatment of earlier stages of lung disease with 1 mg per kg of prednisone on alternate days for as long as two-year cycles appears to be a promising new therapy. Further studies of the use of inhaled corticosteroids seem warranted to see if toxicity can be further limited while retaining efficacy.

If steroid therapy is effective, can nonsteroidal anti-inflammatory agents also favorably affect earlier stages of cystic fibrosis lung disease without the unwanted steroid side effects? A recently concluded four-year, double-blind, placebo-controlled trial of the use of high-dose ibuprofen showed a similar efficacy—virtually halting progressive lung function deterioration without any important toxic effects. In this study, however, it was clear that each patient needs an individually tailored pharmacokinetic evaluation to achieve a target peak plasma concentration of drug to suppress neutrophil ingress and activation in vivo. Plans are being made to provide a clinically useful pharmacokinetic analytic package to determine proper dosages.

In tandem with approaches to broadly suppress inflammation, efforts have been made to target specific mediators of inflammation, such as neutrophil elastase and other proteases. For this purpose, infused or inhaled antiproteases such as $\alpha_1$-protease inhibitor ($\alpha_1$-antitrypsin), recombinant human secretory leukoprotease inhibitor, and various synthetic peptide antiproteases have entered clinical trials. It appears that achieving concentrations of these suppressors sufficient to fully buffer the enormous load of free proteases in cystic fibrosis airways is the principal limiting factor to this approach. Drugs that suppress neutrophil activation, such as orally administered pentoxifylline, show promise.

In concert with inflammatory damage, ingress and activation of neutrophils result in a large burden of dying cells that release structural components into the airways. DNA and actin are two such structural components that are present in high concentrations and result in pronounced increases in viscoelasticity and adhesion tension of airways secretions. The genes for human deoxyribonuclease and gelsolin (the latter being a natural human protein that depolymerizes actin in a manner analogous to deoxyribonuclease's cleavage of DNA strands) have now been cloned, and recent clinical trials of recombinant human deoxyribonuclease (Pulmozyme, Genentech) have shown that, in patients with cystic fibrosis with mild to moderate lung disease, treatment can improve lung function by 5% to 10% for at least two years and reduce the frequency of pulmonary exacerbations requiring intravenous antibiotic therapy by 25% to 33%. Deoxyribonuclease was approved for use in patients with cystic fibrosis in early 1994, and it is safe and effective in patients with severe lung disease (forced vital capacity < 40% of predicted) and can also be used in patients during pulmonary exacerbations. Major questions regarding the future use of Pulmozyme include its role in early disease (children < 6 years or persons with normal or near-normal pulmonary function) and its long-term effect on the course of cystic fibrosis lung disease. Clinical trials of recombinant human gelsolin, which shows potent mucolytic activity and appears to be synergistic with Pulmozyme in vitro, are anticipated in 1995.